

PATENT  
USSN 09/732,348  
674538-2001

AMENDMENT

Please amend the application, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows:

IN THE SPECIFICATION

Please amend the specification, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows:

Page 1, line 5 to page 2, line 12, please rewrite the paragraph thereat as follows:

*B* This application is a continuation-in-part of PCT application no. PCT/GB00/02071 entitled "GENE SWITCHES" filed 30 May 2000 and published on December 7, 2000 as WO 00/73434, designating the US and claiming priority from GB applications 9912635.1 filed 28 May 1999 and Great Britain applications 0001580.0 and 0001578.4, both of which were filed 24 January 2000. Further mentioned and incorporated by reference herein are PCT/GB99/03730, filed November 9, 1999, published as WO00/27878A1 on May 18, 2000 entitled "Screening System For Zinc Finger Polypeptides For A Desired Binding Ability" and claiming priority from GB application 9824544.2, filed November 9, 1998, and designating the US; PCT/GB99/03730 which is a continuation-in-part of US patent application Serial No. 09/139,762, filed August 25, 1998 (now US Patent No. 6,013,453), which is a continuation of US patent application Serial No. 08/793,408 (now US Patent No. 6,007,988), filed as PCT application no. PCT/GB95/01949 on August 17, 1995, designating the U.S. and, published as WO96/06166 on February 29, 1996 entitled "Improvements in or Relating to Binding Proteins for Recognition of DNA"; PCT/GB95/01949 claims the benefit of priority from GB application 9514698.1, filed July 18, 1995, GB application 9422534.9, filed November 8, 1994 and GB application no. 9416880.4, filed August 20, 1994. Mention is also made of: USSN 08/422,107; WO96/32475; WO99/47656A2, published September 23, 1999 entitled "Nucleic Acid Binding Proteins"; WO98/53060A1, published November 26, 1998 entitled "Nucleic Acid Binding Proteins"; WO98/53059A1 published November 26, 1998 entitled "Nucleic Acid Binding Proteins"; WO98/53058A1 published November 26, 1998 entitled "Nucleic Acid Binding Proteins"; WO98/53057A1 published November 26, 1998 entitled "Nucleic Acid Binding Polypeptide Library"; US Patent Nos. 6,013,453 and 6,007,988; Fiehn et al. (2000) Nature Biotechnol. 18:1157-1161; Richter et al. (2000) Nature Biotechnol. 18:1167-1171; and, generally, Nature

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Pages 11-12, please rewrite the text of the second full paragraph on page 11 and the paragraph bridging pages 11-12, and the first full paragraph on page 12 as follows:

--In general, a preferred zinc finger framework has the structure:

(A)  $X_{0-2} C X_{1-5} C X_{9-14} H X_{3-6} H/C$

where X is any amino acid, and the numbers in subscript indicate the possible numbers of residues represented by X.

In a preferred aspect of the present invention, zinc finger nucleic acid binding motifs may be represented as motifs having the following primary structure:

(B)  $X^a C X_{2-4} C X_{2-3} F X^c X X X L X X H X X X^b H$  - linker

wherein X (including  $X^a$ ,  $X^b$  and  $X^c$ ) is any amino acid.  $X_{2-4}$  and  $X_{2-3}$  refer to the presence of 2 or 4, or 2 or 3, amino acids, respectively, and  $X X X X L X X H X X$  between  $X^c$  and  $X^b$  are designated positions -1, 1, 2, 3, 4, 5, 6, 7, 8, and 9. The Cys and His residues, which together coordinate the zinc metal atom, are marked in bold text and are usually invariant, as is the Leu residue at position +4 in the  $\alpha$ -helix.

Modifications to this representation may occur or be effected without necessarily abolishing zinc finger function, by insertion, mutation or deletion of amino acids. For example it is known that the second His residue may be replaced by Cys (Krizek *et al.*, (1991) J. Am. Chem. Soc. 113:4518-4523) and that Leu at +4 can in some circumstances be replaced with Arg. The Phe residue before  $X^c$  may be replaced by any aromatic other than Trp. Moreover, experiments have shown that departure from the preferred structure and residue assignments for the zinc finger are tolerated and may even prove beneficial in binding to certain nucleic acid sequences.